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In The
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

**On Writ Of Certiorari To
The Vermont Supreme Court**

BRIEF OF *AMICI CURIAE* DAVID B. ROSS, M.D., Ph.D. AND STEFAN P. KRUSZEWSKI, M.D. IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICI CURIAE*[1]

Amici curiae are physicians who have performed extensive work in the public and private sectors researching, evaluating, and bringing to public light information pertaining to the safety and efficacy of prescription drugs. *Amici* have a strong interest in the federal preemption issue before the Court in this case based on their and their colleagues' direct involvement with government regulation and private marketing of prescription drugs. *Amici* believe that the resolution of this case could have a significant impact on the health and safety of patients and the public at large who depend on state tort law and other public processes to help ensure the safety and efficacy of prescription drugs that are approved for specific uses by the Food and Drug Administration ("FDA"). *Amici* thus submit this brief in support of Respondent urging the Court to hold that the FDA's approval of a prescription drug's label does not preempt state tort law claims for failure to warn consumers of health and safety risks caused by the drug.

Dr. David B. Ross received his M.D. and Ph.D. (Biochemistry) from the New York University School of Medicine. After completing a categorical internal

[1] Letters granting blanket consent to the filing of *amicus curiae* briefs have been filed with the Clerk. This brief was not authored in whole or in part by counsel for a party. No person or entity other than *amici curiae* or their counsel made a monetary contribution to the preparation or submission of this brief.

medicine residency at NYU, Dr. Ross received fellowship training in infectious diseases at Yale University School of Medicine, and subsequently was a member of the faculty there. From 1996 until 2006, Dr. Ross served as a medical officer at the FDA, first as a medical reviewer and team leader in FDA's division of Anti-Infective Drug products, then as deputy director of the FDA office reviewing therapeutic biologic products (Office of Drug Evaluation VI), and subsequently as associate director of FDA's Office of Oncology Drug Products. During his time at FDA, Dr. Ross was involved in the review of a number of high-profile drug applications, including the first new class of antibiotics to be approved in three decades, the first monoclonal antibody used to treat multiple sclerosis, and the first oral drug for treatment of iron overload. He also worked extensively on medical countermeasures against biological weapons. Since 2006, Dr. Ross has been Director of Clinical Public Health Programs at the Department of Veterans Affairs, where he oversees the Department's National HIV and Hepatitis C Programs. Dr. Ross also holds an appointment as Associate Clinical Professor of Medicine at George Washington School of Medicine and Health Sciences. Dr. Ross's article, *The FDA and the Case of Ketek*, 356 N. ENG. J. MED. 1601 (Apr. 19, 2007), is cited and discussed extensively herein.

Dr. Stefan P. Kruszewski received his M.D. from Harvard Medical School in 1977. He then completed a Medical Internship at New England Deaconess Hospital, a Psychiatric Residency and Fellowship

at the University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School, and a Mini-Fellowship at Duke University. He subsequently served as Chairman of the Department of Psychiatry at Conemaugh Memorial Hospital in Johnstown, Pennsylvania and as Director of the Geriatric Neuropsychiatric Institute and Associate Director of Psychiatric Residency at the Allegheny Neuropsychiatric Institute, an affiliate of Allegheny General Hospital in Pittsburgh. Starting in 2001, Dr. Kruszewski served as Psychiatric Consultant for the Pennsylvania Department of Public Welfare, where he performed medical reviews of the services provided by treatment facilities, including their use of prescription medications. He was terminated from this position after reporting systemic abuses at these facilities, including widespread and improper prescriptions of antipsychotic medications for off-label uses. Dr. Kruszewski also has served on the faculty of Eastern University and the Penn State College of Medicine. Dr. Kruszewski was recognized as a "distinguished" expert whose testimony was deemed admissible in the mass tort case *In re Zyprexa Products Liability Litig.*, 489 F. Supp. 2d 230, 287 (E.D.N.Y. 2007), involving a prescription antipsychotic drug whose safety and off-label uses are discussed herein.

Amici submit this brief to inform the Court about the deficiencies and abuses that they and their colleagues have witnessed and brought to light through their involvement with the FDA's prescription drug approval process and the subsequent marketing of

these drugs. *Amici* believe that the deficiencies and abuses discussed herein help demonstrate that adoption of Petitioner's and its *amici*'s sweeping federal preemption arguments would undermine the public health and safety goals of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 *et seq*.

INTRODUCTION AND SUMMARY OF ARGUMENT

Petitioner's argument (Brief at 40) that the FDA functions as an "expert scientific agency [that] makes uniform, national judgments about the safety and effectiveness of prescription drugs by balancing therapeutic benefits against safety risks," and, in so doing, acts as the "ultimate regulator of the labeled conditions of use for which a drug is approved," is not borne out as a matter of law or fact. Respondent (Brief at 25-31) demonstrates the lack of statutory support for this argument, and *amici* will not repeat her analysis, save to emphasize that there has been no showing of a "'clear and manifest'" intent by Congress to make FDA the exclusive regulator of prescription drug safety by preempting a field that, at least to the extent of compensating injury victims, has been "'traditionally occupied by the States.'" *English v. General Electric Co.*, 496 U.S. 72, 79 (1990), quoting *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (internal citation omitted). Indeed, Congress's intent *not* to enact a sweeping preemption regime for prescription drug safety is proven by the

fact that Congress expressly stated its intent elsewhere in the FDCA to preempt state laws pertaining to medical devices, 21 U.S.C. § 360k(a), while expressing no such intent with regard to drug labeling. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008); *cf. Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 449 (2005) (addressing statute's express preemption language as basis for rejecting product manufacturer's field preemption argument).

Instead, this brief focuses on specific examples that show the FDA's failure or inability to carry out its statutory duty of ensuring prescription drug safety and efficacy in order to highlight the adverse public health and safety consequences that would result from these preemption arguments. The FDA is charged by statute with "ensuring that . . . human and veterinary drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). But the FDA has repeatedly failed to carry out these mandates at both the drug-approval and the post-approval marketing stages of its regulatory process.

At the approval stage, the FDA routinely fails to require sufficient and reliable evidence that is necessary to ensure that prescription drugs are safe and effective before they are marketed. *See*, *generally*, Carpenter, *et al.*, *Drug-Review Deadlines and Safety Problems*, 358 N. ENG. J. MED. 1354, 1359 (Mar. 27, 2008). For example, the FDA approved the antibiotic Ketek for marketing in 2004 despite the fact that the safety tests ordered by its advisory committee had resulted in submissions of fabricated safety data – a

fact that FDA officials *deliberately withheld from the advisory committee that was reviewing Ketek and recommended its approval*. *See* Ross, *supra*, at 1602. Within three years of its approval, Ketek was linked to dozens of cases of acute liver failure, at least four of which resulted in death, while serious questions persisted about the drug's efficacy. *See id*. at 1602-03.

At the post-approval marketing stage, the FDA is widely recognized as lacking the resources and capacity for effective regulation of drugs whose hazards become apparent after there is widespread use in the market. An example of the FDA's failure in this regard is the agency's inability to prevent unlawful promotion of unapproved uses of prescription drugs. *See* U.S. Gov't Accountability Office, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses*, GAO-08-835, at 5-16 (July 2008) (finding that FDA lacks any formal process for tracking drug promotion submissions, has extremely limited staffing, and lacks any separate oversight activity for off-label uses). The FDA's inability to enforce the statutory prohibition against promotions for off-label uses, *see* 21 U.S.C. § 331(a) and (d), is illustrated in the case of the antipsychotic drug Zyprexa. The FDA approved Zyprexa in 1996 for treatment of adult schizophrenia and bipolar disorder. But its manufacturer was shown, largely through documents obtained in private tort and state Medicaid litigation, to have encouraged promotion of off-label uses such as treatment of pediatric conditions, dementia, and dementia-related psychosis for which

its effectiveness was never demonstrated to the FDA. *See* Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. Times, Dec. 18, 2006; Berenson, *Lilly E-Mail Discussed Off-Label Drug Use*, N.Y. Times, Mar. 14, 2008. At the same time, as Zyprexa was being prescribed to tens of millions of patients worldwide, there was substantial evidence linking antipsychotic drugs to the onset of diabetes and excessive weight gain, neither of which was mentioned on Zyprexa's originally approved warning label. *See In re Zyprexa Products Liability Litig.*, *supra*, at 249-53.

In light of these and other well documented failures by the FDA to ensure the safety and efficacy of approved prescription drugs, the Court should reject Petitioner's and its *amici*'s sweeping preemption arguments that would make the FDA the nation's sole regulator of drug safety. Such a result would be contrary – and indeed detrimental – to the health and safety goals of the FDCA itself.

ARGUMENT

I. THE FDA'S APPROVAL OF KETEK AND AVANDIA DEMONSTRATES A FAILURE TO ENSURE PRESCRIPTION DRUG SAFETY AND EFFICACY.

Petitioner's and its *amici*'s arguments for vesting exclusive authority in the FDA to regulate prescription drug labeling and safety are predicated upon

unfounded assumptions about the agency's ability and willingness to demand sufficient proof of safety and efficacy before it approves drugs for marketing. In fact, the past decade alone has witnessed a number of instances where high-profile prescription drugs approved by the FDA were shown to pose life-threatening health risks to patients. *See* Curfman, *et al.*, *Why Doctors Should Worry About Preemption*, 359 N. ENG. J. MED. 1, 2 (July 3, 2008). Whether or not these cases by themselves demonstrate failures by the FDA, a closer look at two recently approved drugs raises serious questions about the agency's ability and willingness to ensure the safety and efficacy of prescription drugs before they are marketed.

First, the process through which the FDA granted approval of the antibiotic Ketek demonstrates a serious failure to demand sufficient and reliable evidence of either the product's safety or its efficacy. Ketek was presented as the first of a new class of antimicrobial agents that circumvent antibiotic resistance. Ross, *supra*, at 1601. In its initial review, the FDA's advisory committee asked Ketek's manufacturer to conduct a study to obtain additional safety data for patients likely to use the drug, in part based on concerns about an apparent association with liver damage. *Id*. The ensuing study of Ketek, known as "study 3014," compared the incidence of hepatic, cardiac, and visual adverse events in patients taking Ketek with those in patients taking an approved therapy. *Id*. This study was conducted over five months, with more than 24,000

subjects, and purported to show that Ketek was as safe as the comparison treatment. *Id*.

In fact, FDA inspections of the largest testing sites identified serious concerns of fraud, resulting in referrals of four of the largest sites for criminal investigation. *Id*. at 1602.[2] The physician who enrolled the most patients, more than 400, was found to have completely fabricated patient data and was sentenced to 57 months in prison for her fraudulent conduct in this testing. *Id*. at 1601-02; *see also* Letter from Senator Charles E. Grassley, Chair U.S. Senate Committee on Finance, to FDA Commissioner Andrew C. Von Eschenbach, Dec. 13, 2006 ("Grassley Letter") at 4-9. The FDA's Office of Criminal Investigation ("OCI") initially recommended to the drug Review Division and the Division of Scientific Investigation ("DSI") that "careful consideration" be given to use of data from this physician's testing site. Grassley Letter at 8. A DSI official raised further concerns about the second and third largest testing sites, including investigatory findings of over-enrollment, inadequate safety-related documentation, untimely record keeping, and improper shipping of laboratory samples. *Id*. at 10. Other "red flags" raised

[2] The discovery of these site deficiencies appears to be fortuitous in light of recent findings that the FDA inspects fewer than one percent of new drug and device testing sites. *See* Department of Health and Human Services Office of Inspector General, *The Food and Drug Administration's Oversight of Clinical Trials*, OEI-01-06-00160 at 19 (Sept. 2007).

by study 3014 included the manufacturer's decision to exclude testing data from two other sites and a widespread failure to adhere to the study's patient enrollment protocol for test sites. *Id*. at 11.

Faced with these irregularities and concerns about fraudulent data, the FDA's Review Division could have refused to submit the study 3014 data to the Ketek advisory committee, as the official charged with presenting the data recommended. *Id*. at 14. Alternatively, it could have submitted the data along with the evidence of fraud uncovered by the ongoing criminal investigations. But instead, the Review Division chose a third option. It presented study 3014 to the advisory committee in January 2003 *without disclosing or making any mention whatsoever of the data irregularities and ongoing criminal fraud investigation*. *Id*. at 2-3, 5-6. Unaware of these problems with the reliability of the safety data before it, the advisory committee voted 11 to 1 to recommend approval of Ketek. *Id*. at 5-6.

In deciding to submit the study 3014 results without disclosing the ongoing fraud investigation, the Review Division's Office Director stated that "*I don't believe spending time on these issues in front of the [advisory committee] will be productive.*" *Id*. at 7 (emphasis added). The DSI's Division Director later contended that releasing information from an ongoing criminal investigation "would not only have been unprecedented and a violation of due process, but also would not have provided any meaningful context for committee consideration." *Id*. at 17. Four years after

this occurred, FDA officials stood by the decision to conceal evidence and concerns about fraudulent safety data from the advisory committee, explaining in response to Dr. Ross's article that "*[t]he FDA did not discuss data-integrity issues at the second advisory committee meeting to avoid compromising the ongoing investigations . . .* " Soreth, *et al.*, *Ketek – The FDA Perspective*, 356 N. ENG. J. MED. 1675 (April 19, 2007). But this does not explain why, given concerns over the reliability of the testing data and allegations about the process by which it was gathered, FDA officials decided to present study 3014 to the advisory committee *at all* while these investigations were still in progress. Ross, *supra*, at 1602.

Subsequent FDA reviews of Ketek's safety and efficacy were likewise based on problematic data. For example, the agency relied on foreign post-marketing reports on Ketek as evidence of its safety, without verifying their accuracy or completeness, even though these reports typically do not serve as a primary basis for determining safety. *Id*. Similarly, in assessing Ketek's efficacy, the agency relied on "noninferiority trials" that are meant not to demonstrate a product's superiority to existing treatments, but rather to show the "maximum margin by which the new invention may be less effective than older inventions but still be considered better than placebos." *Id*. By 2004, when Ketek was nearing final approval, the use of noninferiority trials to demonstrate a drug's efficacy was considered unsound. *Id*.; *see also* Powers, *Noninferiority and Equivalence Trials: Deciphering 'Similarity'*

of Medical Interventions, 27 STATISTICS IN MEDICINE 343 (Feb. 10, 2008) ("Inappropriate [noninferiority] trials have great clinical relevance since they may lead to approval by regulatory agencies of medical interventions whose benefits compared with placebo are unclear, and can start investigators down a slippery slope of comparing one potentially ineffective intervention to another in perpetuity."). The agency's rationale for accepting use of noninferiority trials in the case of Ketek was the need to stand by earlier agreements with the drug's sponsor. Ross, *supra,* 1602-03; Soreth, *supra*, 1675.

The FDA's approval of Ketek in 2004 thus was based in significant part on fraudulent safety data and other unreliable evidence as to the product's efficacy. In light of this checkered FDA approval history, the results of Ketek's use on patients are not surprising. Within seven months of the drug's launch, the first death of a Ketek user from liver failure was reported in a patient being treated for a mild respiratory tract infection. *See* Ross, *supra*, at 1603. Less than a year later, a single medical center reported a cluster of three cases of Ketek-associated liver failure, one fatal. *Id*. Nonetheless, the FDA continued to trumpet Ketek's safety, *citing study 3014 as evidence for this assertion. Id*. By the end of 2006, Ketek was associated with 53 cases of hepatotoxic effects, including 23 cases of acute severe liver injury, and 12 cases of acute liver failure, four of which were fatal. *Id.*

The FDA's approval of Ketek for marketing in the absence of reliable safety or efficacy data is not

unique. In 1999, the FDA approved the "wonderdrug" Avandia (rosiglitazone) for treatment of hyperglycemia for type 2 diabetes. Psaty and Furberg, *Rosiglitazone and Cardiovascular Risk*, 356 N. ENG. J. MED. 2522 (June 14, 2007). At the time of its approval, Avandia had been shown through small, short-term (up to 26 week) trials to reduce levels of fasting glucose and glycated hemoglobin by about one percent. *See id*. at 2522-23. But this result was not measured against the drug's longer term health effect in causing increase in body weight, fluid retention, and anemia. *See id*. Instead, the FDA approved the drug without the benefit of any long-term studies on its overall health effects on diabetics, and the drug was soon being prescribed to millions of patients. *See id*. at 2523.

In June 2007, eight years after FDA approval, a meta-analysis of treatment trials concluded that Avandia was associated with a significant (43%) increase in risk of heart attack and a slight increase in risk of death from cardiovascular causes. Nissen and Wolski, *Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death From Cardiovascular Causes*, 356 N. ENG. J. MED. 2451, 2457 (June 14, 2007). This meta-analysis of Avandia echoed the view that the trial studies "were not adequately powered to determine the effects of this agent on microvascular or macrovascular complications of diabetes, including cardiovascular morbidity and mortality." *Id*. at 2458. The authors recognized that even their own data were incomplete and that there still was an "urgent

need for comprehensive evaluations to clarify the cardiovascular risks of [Avandia]." *Id*. at 2469. Despite these limitations, the authors concluded that Avandia was associated with a significant increase in the risk of heart attack and a borderline increase in risk of death from cardiovascular causes. *Id*. at 2467.

Analysts looking at this study of an undertested but nevertheless approved drug used by tens of millions of patients concluded that Avandia "represents a major failure of the drug-use and drug-approval processes in the United States." Psaty and Furberg, *supra*, 2523. The chair of the FDA's post-approval advisory committee for Avandia concurred:

> The basic plot of the rosiglitazone story quickly became obvious to the advisory committee: a new 'wonder drug,' approved prematurely and for the wrong reasons by a weakened and underfunded government agency subjected to pressure from industry, had caused undue harm to patients.

Rosen, *The Rosiglitazone Story – Lessons From an FDA Advisory Committee*, 357 N. ENG. J. MED. 844 (Aug. 30, 2007).

Despite the FDA's ongoing investigation of Avandia, agency officials appear to remain determined to turn a blind eye to the serious health risks associated with Avandia. In March 2006, an FDA drug safety supervisor approved a reviewer's recommendation of a black box warning for Avandia on the risk of swelling that could lead to heart failure. *See* Saul and

Harris, *Diabetes Drug Still Has Heart Attack Risk, Doctors Warn*, N.Y. Times, June 6, 2007. But the supervisor reported that FDA officials overruled her decision, ordered her to retract her approval of the black box warning, and removed her from future supervisory reviews of Avandia. *Id*.

The FDA's approval of Ketek and Avandia should give the Court serious pause when considering the health and safety implications of Petitioner's and its *amici*'s sweeping preemption arguments. In both cases, the FDA pushed the drugs through to marketing approval despite an absence of reliable evidence of long-term safety and efficacy. Both cases also reveal FDA officials' willingness to ignore agency professionals in their determination to bring drugs to market or to keep them on the market, as both Ketek and Avandia are to this day. In light of these and other examples of the FDA's failure or inability to ensure the safety and efficacy of prescription drugs, the Court should reject the arguments for preempting application of state tort law to approved prescription drugs as contrary to the public health and safety concerns that underpin the FDCA itself.

II. THE FDA's INABILITY TO PREVENT OFF-LABEL PROMOTION OF PRESCRIPTION DRUGS FURTHER SHOWS THE AGENCY'S FAILURE TO ENSURE DRUG SAFETY AND EFFICACY.

The FDA also has failed to ensure prescription drug safety and efficacy through its regulation of

post-approval marketing. The FDCA and the FDA's implementing regulations prohibit manufacturers from marketing or promoting prescription drugs for "off-label" uses not approved by the FDA. *See* 21 U.S.C. § 331(a) and (d); 21 C.F.R. § 202.1(e)(4). This prohibition serves important safety-related purposes that implicate the effectiveness of the FDA's entire prescription drug approval system. As one commentator explains:

> [O]ff-label use has potentially negative consequences. It undercuts expectations that drug safety and efficacy have been fully evaluated. When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies – and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.

Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 N. ENG. J. MED. 1427, 1427-28 (April 3, 2008). The off-label marketing ban is thus an important drug safety measure because it prevents manufacturers from promoting drug uses that are unsupported by evidence of efficacy that the FDA would require to overcome known and unknown health and safety risks.

Despite the off-label marketing ban's importance to the FDA's regulatory regime, the agency's failure to

enforce this prohibition is widely recognized as a systemic problem. The Government Accountability Office's recent study, *Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses*, GAO-08-835 (July 2008), concluded that:

- As of March 2008, the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") had the equivalent of 44 full-time staff devoted to overseeing all prescription drug promotion (*id*. at 9);
- during the calendar years 2003 through 2007, DDMAC received approximately 277,000 final promotional materials from drug companies, including 68,000 in 2007 alone (*id*. at 15-16);
- DDMAC lacks a system or process to consistently track its receipt and review of submitted promotional materials; (*id*.);
- the FDA has no separate oversight activities designed specifically for off-label promotion (*id*. at 5); and that
- the FDA itself acknowledges that it can only review a small portion of submitted promotional materials (*id*. at 13).

In light of these limitations on the FDA's ability to regulate off-label prescription drug use, it is hardly surprising that a commentator recently found that, "more and more frequently, *it is not FDA action but litigation that raises important questions about*

off-label drug prescribing." Stafford, *supra*, at 1428 (emphasis added). The antipsychotic drug Zyprexa and the epilepsy drug Neurontin represent two such instances where private litigation brought to light promotion of off-label uses for prescription drugs with significant public health implications.

First, evidence showing promotion of the antipsychotic drug Zyprexa for off-label uses came to light through private tort and state Medicaid litigation over the drug's association with diabetes, hyperglycemia, and excessive weight gain. The FDA approved Zyprexa in 1996 for treatment of adults with schizophrenia and bipolar disorder. *See In re Zyprexa*, 489 F. Supp. 2d at 248. Over the next decade, Zyprexa was prescribed to approximately 20 million patients worldwide. *See* Berenson, *Drug Files Show Maker Promoted Unapproved Use*, N.Y. Times, Dec. 18, 2006. Between 1999 and 2002 alone, Zyprexa's sales revenues doubled from $1.5 billion to $3 billion. *Id*. During this time, the American Diabetes Association and other public health groups demonstrated that there was considerable evidence linking treatment with atypical antipsychotics such as Zyprexa to increased risk of diabetes and hyperglycemia and rapid increase in body weight. *See In re Zyprexa*, 489 F. Supp. 2d at 249-50.[3]

[3] The FDA first required a package insert warning about risk of diabetes and hyperglycemia in late 2003, *id*. at 248, but did not address changes to the warning label itself until 2007, four or more years after Japanese, European, Australian, and Canadian regulators required similar label warnings. *Id*. at 250-51.

As a result of tort litigation brought by Zyprexa patients and state Medicaid reimbursement litigation, it was discovered that Zyprexa's manufacturer engaged in a multi-year promotional campaign involving off-label uses of the drug. As part of its "*Viva Zyprexa*" campaign starting in late 2000, the manufacturer identified *primary care* doctors as a market for prescribing Zyprexa, notwithstanding the fact that its only two approved uses (schizophrenia and bipolar disorder) are treated primarily by *psychiatrists*. *See* Berenson, *Drug Files*, *supra*. In 2003, despite the fact that the drug's approval was limited to treatment of adult schizophrenia and bipolar disorder, an executive vice president issued a message proclaiming that Zyprexa was "getting traction with some neurologists for treatment of pain," and that "we must seize the opportunity to expand our work with Zyprexa in the child-adolescent population." *See* Berenson, *Lilly E-mail Discussed Off-Label Drug Use*, N.Y. Times, March 14, 2008.[4] Both of these were off-label uses for which there was no showing of effectiveness to the FDA that could even conceivably justify approval in the face of the health risks associated with Zyprexa. *Cf.* Kruszewski and Paczynski, *Atypical Antipsychotic Agents for the Schizophrenia Prodome: Not a Clear First Choice*, 20 INT'L J. OF RISK

[4] This information came to light in a lawsuit filed by the State of Alaska seeking to recover from the manufacturer the Medicaid costs the state paid for treating Zyprexa patients who developed diabetes. *Id*.

& SAFETY IN MED. 37 (May 2008) (noting paucity of evidence supporting use for adolescents and young adults).

A second case in which privately initiated litigation exposed even greater evidence of promotion for off-label uses involved the epilepsy drug Neurontin. The FDA approved Neurontin in 1993 solely for combination use with other drugs to control epileptic seizures. *See Drugmaker to Pay $430 Million in Fine, Civil Damages*, FDA Consumer (July-Aug. 2004) (hereafter, "*Drugmaker to Pay*"). Dr. David Franklin worked as a "medical liaison" for Neurontin's manufacturer, the Parke-Davis division of Warner-Lambert Co., for five months in 1996 during which company officials trained him and other liaisons to promote various off-label uses at daily dosages that more than doubled the maximum dosage approved by the FDA. *See United States ex rel. Franklin v. Parke-Davis, Div. of Warner-Lambert Co.*, 147 F. Supp. 2d 39, 45-46 (D. Mass. 2001). In August 1996, after he left Parke-Davis, Dr. Franklin filed a nine-count *qui tam* complaint alleging that Parke-Davis engaged in a fraudulent scheme to promote sales of Neurontin for off-label uses, resulting in submissions of false claims to the Veterans Administration and for Medicaid reimbursement that disguised off-label uses as approved. *Id*. at 43. The United States joined the action as *amicus curiae*, *id*. at 46, and Dr. Franklin's claims survived a motion for summary judgment. *See United States ex rel. Franklin v. Parke-Davis, Div. of*

Warner-Lambert Co., 2003 U.S. Dist. LEXIS 15754 (D. Mass. Aug. 22, 2003).

The United States also launched a criminal investigation based on Dr. Franklin's allegations, and concluded that Warner-Lambert was promoting Neurontin for the off-label treatment of bipolar disorder, pain disorders, Lou Gehrig's disease, attention-deficit disorder, migraines, drug and alcohol withdrawal seizures, and restless leg syndrome, as well as for first-line monotherapy treatment of epilepsy. *See Drugmaker to Pay*, *supra*. Prosecutors further alleged that Warner-Lambert encouraged sales representatives to mislead doctors about the scope of Neurontin's FDA approval, the drug's efficacy, and about their own scientific credentials. *Id*. The government also alleged that Warner-Lambert paid physicians to allow sales representatives to accompany them to see patients, and offer patients treatment advice favoring use of Neurontin. *Id*. As a result of Dr. Franklin's *qui tam* action and the criminal investigation that it sparked, Warner-Lambert pled guilty to two counts of misbranding under the FDCA, paid a $240 million criminal fine and $83.6 million in civil damages, and paid $38 million in additional damages to the 50 states. *Id*.

The Zyprexa and Neurontin cases bear out the earlier-discussed criticism that, "more and more frequently, it is not FDA action but litigation that raises important questions about off-label drug prescribing." Stafford, *supra*, at 1428. In both cases, it was not FDA officials charged with enforcing the

statutory and regulatory ban on promoting off-label uses, but private and state government litigants who brought to light serious evidence of off-label prescription drug promotion. In the case of Zyprexa, this evidence came to light after the drug had been prescribed to tens of millions of users worldwide and was linked with development of diabetes and rapid weight gain.

The critical role that private litigation has played in uncovering and policing off-label prescription drug promotion only further counsels against adoption of Petitioner's and its *amici*'s sweeping arguments for preempting state tort law. Given the FDA's failure and inability to enforce this critical component of the regulatory system for ensuring prescription drug safety and efficacy, the Court should reject these preemption arguments as contrary to the public health and safety goals of the FDCA itself.

CONCLUSION

For the reasons set forth herein, the Vermont Supreme Court's decision rejecting Petitioner's pre-emption defense should be affirmed.

Respectfully submitted,

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